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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,215	03/27/2001	Scott A. Waldman	TJU-2441/OTT-3263-4	2195

7590 06/10/2003

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EXAMINER
SPIEGLER, ALEXANDER H

ART UNIT	PAPER NUMBER
1637	15

DATE MAILED: 06/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/820,215	WALDMAN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *16-31 and 33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6-9,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-15 and 32) in Paper No. 13, filed on February 25, 2003 is acknowledged. Applicants argue Group III (claim 31) should be reconfigured so that Group I and III is contained within a single group; Applicants argue that a search of Group I "would necessarily lead to disclosures, to the extent any exist, of the methods defined by the claim of Group II".

Group III (claim 31) is drawn to a "method of detecting the presence of a tissue-specific marker in a sample not associated with the expression of the tissue specific marker". This claim requires a search of finding "a tissue-specific marker in a sample *not* associated with the expression of the tissue-specific marker" (emphasis added). Group I (claim 32, for example) is specifically drawn to "detecting the presence of mRNA that encodes a marker *associated with the disseminated cell*" (emphasis added). Accordingly, because these Groups require searching for different markers (i.e., one marker which *is* associated with a disseminated cell sample, and one maker *not* associated with the sample), Applicants' arguments are found to be unpersuasive, and thus, the restriction requirement is maintained.

2. Claims 1-36 are pending, claims 1-15 and 32 have been examined on the merits, and claims 16-31 and 33-36 have been withdrawn as being drawn to a non-elected invention. (See CFR 1.142(b)).

Sequence Notes

3. The Sequence Listing filed in this application complies with the requirements of 37 CFR 1.821-1.825 and has been entered.

Information Disclosure Statement

4. The information disclosure statements of Paper Nos. 6-9, 11 and 14 comply with CFR 1.97, 1.98, and M.P.E.P. 609, and has been considered. It is also noted that references that were not forwarded to the US PTO have not been considered. (See attached PTO-1449s)

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 15 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 15 over "the disseminated cell" because it lacks antecedent basis, as claim 1 (from which claim 15 depends from) is drawn to a "disseminated cell marker". However, Applicants could amend the claim to recite, "wherein the disseminated cell marker is a marker for a metastatic colon cancer cell".

B) Claim 32 over "a marker associated with the disseminated cell" because it is not clear as to what is meant or encompassed by this recitation.

MPEP 2173.02 discusses 35 U.S.C. 112, 2nd paragraph:

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;
(B) The teachings of the prior art; and
(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000)... If the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, a rejection of the claims under 35 U.S.C. 112, second paragraph is appropriate. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973).

In the instant case, the recitation of "a marker associated with the disseminated cell" is not found in any patent or patent application, except that of the instant application and its corresponding WO document, WO 200173131. On page 12, the specification discusses "disseminated cell markers", but fails to define a marker "associated" with a disseminated cell. The specification does not specify as to how one determines whether a marker is "associated" with a disseminated cell. Accordingly, the prior art, the specification and the claims fail to set out and circumscribe "a marker associated with the disseminated cell" with a reasonable degree of clarity and particularity.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-15 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting the presence of a disseminated **epithelial** cell marker in a sample, comprising eliminating illegitimate transcription-positive cells from the sample **by removing CD34+ cells**, does not reasonably provide enablement for detecting the presence of a disseminated **any** cell marker in a sample, comprising eliminating illegitimate transcription-positive cells from the sample **by any means**. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

Also, MPEP 2164.01 states:
"Even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)."

The *Wands* court outlined several factors to be considered in determining whether a disclosure would require undue experimentation:

"They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) The quantity of experimentation necessary

In order to practice the invention, the practitioner must detect the presence of any disseminated cell marker in any sample by eliminating illegitimate transcription-positive cells from said sample, and then detect the presence of mRNA that encodes said marker.

This involves, at least, 1) determining methods for eliminating illegitimate transcription-positive cells; and 2) determining which type of disseminated cell markers will be detecting using the methods from step 1).

The prior art teaches that illegitimate transcription occurs in any gene in any cell type (see Chelly et al. (PNAS (1989) 86: 2617-21), cited in the IDS; and Chelly et al. (J. Clin. Invest. (1991) 88: 1161-6), also cited in the IDS). Additionally, Doeberitz et al. (Cancer & Metastasis (1999) 18(1): 43-64) teaches some nucleic acid based assays for the detection of rare cancer cells in clinical species (e.g., in mammary carcinoma), "are hampered by illegitimate transcription of the respective marker" and "Thus, before detection of disseminated breast cancer cells enters routine diagnostic practice, significant achievements in establishing specific and sensitive markers and *vigorous quality control are essentially required*" (emphasis added) (pg. 52, col. 1). Also, Salbe et al. (Inter. J. of Bio. Markers (2000) 15(1): 41-3) teaches illegitimate transcription found in normal bone marrow "preclud[es] the use of villin RT-PCR for routine detection of colon cancer cells in bone marrow of patients with colon cancer" (see abstract and pg. 43. Further, Dingermans et al. (Lab. Invest (1997) 77(3): 213-220) teaches, "A serious problem in the detection of tissue-specific transcripts in PBMNC is the detection of illegitimate

transcription levels…although CK-19 may be a useful marker for the detection of lung cancer cells, its application for the detection of circulating tumor cells is not recommended" (see abstract). Accordingly, the prior art teaches illegitimate transcription can occur in any cell, hinders the ability of a skilled artisan to detect cancer cells (i.e., disseminated cell markers), and ultimately, that further experimentation is required to eliminate illegitimate transcription from detection assays.

The claims are drawn broadly to methods of detecting the presence of a disseminated **any** cell marker in a sample, comprising eliminating illegitimate transcription-positive cells from the sample **by any means**.

Given the teachings of the prior art, in essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Therefore, the quantity of experimentation is not only difficult, but also unpredictable.

(2) The amount of direction or guidance presented

The specification teaches only "that CD34+ progenitor cells illegitimately transcribe a variety of epithelial markers", wherein the removal of CD34+ cells enables the detection of epithelial cell markers (see pg. 10, ln. 6-21). The specification also details experiments, which demonstrate that the removal of CD34+ cells provides for the detection of disseminated epithelial markers (pgs. 23-31).

However, the specification is silent to 1) determining methods for eliminating illegitimate transcription-positive cells (other than by removing CD34+ cells); and 2) determining which type of disseminated cell markers (other than disseminated epithelial cell markers) will be detecting using the methods from step 1).

Therefore, the specification is enabled for detecting the presence of a disseminated **epithelial** cell marker in a sample, comprising eliminating illegitimate transcription-positive cells from the sample **by removing CD34+ cells**.

(3) The presence or absence of working examples

Working examples are presented which demonstrate that the removal of CD34+ cells provides for the detection of disseminated epithelial markers (pgs. 23-31). However, there are no examples of alternative methods for eliminating illegitimate transcription-positive cells or alternative disseminated cell markers, which can be detected.

(4) The nature of the invention

The invention is directed to a method of detecting a disseminated cell marker from a sample. Thus, the nature of the invention pertains to genetic screening for detection.

(5) The state of the prior art

The prior art is discussed above (see discussion on "The quantity of experimentation necessary").

(6) The relative skill of those in the art

The level of skill in molecular biology is high, as one of ordinary skill in the art would have to experiment and attempt to find methods for eliminating illegitimate transcription-positive cells (other than by removing CD34+ cells); and determine which type of disseminated cell

markers (other than disseminated epithelial cell markers) will be detecting using the methods from step 1). Not only would this endeavor be time consuming, but also it would be very unpredictable, as the prior art and the specification lack guidance in performing these experiments.

(7) The predictability or unpredictability of the art

Given the teachings of the prior art, and the lack of disclosure in the specification, the ability to eliminate illegitimate transcription by any method, in order to detect any disseminated cell marker is highly unpredictable. (see above)

(8) The breadth of the claims

The invention is directed to methods of detecting the presence of any disseminated cell marker in any sample by eliminating illegitimate transcription-positive cells (by any means) from said sample, and then detect the presence of mRNA that encodes said marker.

Accordingly, in view of the unpredictability in the art and in view of the lack of specific disclosure in the specification, undue experimentation would be required to practice the invention as it is claimed.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3, 5-12, 15 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Kishimoto et al. (EP 0846949, cited in the IDS).

Kishimoto teaches methods for detecting cancer cells by removing CD34+ cells determining the level of mRNA expression of a WT1 gene (see abstract, pgs. 3-5 and 7-10). Specifically, on pages 5, 7 and 9, Kishimoto details that the elimination of CD34+ cells precedes the mRNA expression of the WT1 gene (which is an epithelial cell marker), in order to detect solid cancer cells and atypia. Kishimoto also teaches the WT1 gene is a well-known specific marker of leukemia, but also shows a high level of expression in other cancers unrelated to leukemia (pg. 3, ln. 14-17). Kishimoto further teaches mRNA can be detected by RT-PCR, and WT1 can be detected in a sample selected from the group consisting of, blodd, lymph tissue and bone marrow (pg. 4, ln. 6-22, for example). Kishimoto also teaches WT1 gene can be expressed in other tissue than lung, including the breast and colon (pg. 6). Kishimoto also teaches that CD34+ cells can be removed by using column chromatography (pg. 5, ln. 17-22).

Conclusion

11. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-

3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
June 5, 2003

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
6/5/03